

What the hell is ED?

Einführung und epidemiologische
Konsequenzen

Wirkprinzip, Stoffeigenschaft?

- ▶ Chemikalienrecht (REACH):
- ▶ „Substances of concern“
 - Krebszeugend, erbgutverändernd oder fortpflanzungsgefährdend (CMR)
 - Persistent, sich im Körper anreichernd und giftig (PBT)
 - Sehr persistent und hohe Anreicherung im Körper (vPvBs)
 - Endokrine Disruptoren

Wirkung

Mechanismus

Eigenschaft

Endokrine Disruptoren

- ▶ Stoffe, die durch Veränderung des Hormonsystems die Gesundheit schädigen
- ▶ Wirkmechanismus und Schadfolge
- ▶ OECD Prüfleitlinien:
 - Östrogene, androgene, thyroide und steroidogenetische Wirkungsweise (EATS)
- ▶ Aber... ist EATS wirklich alles?

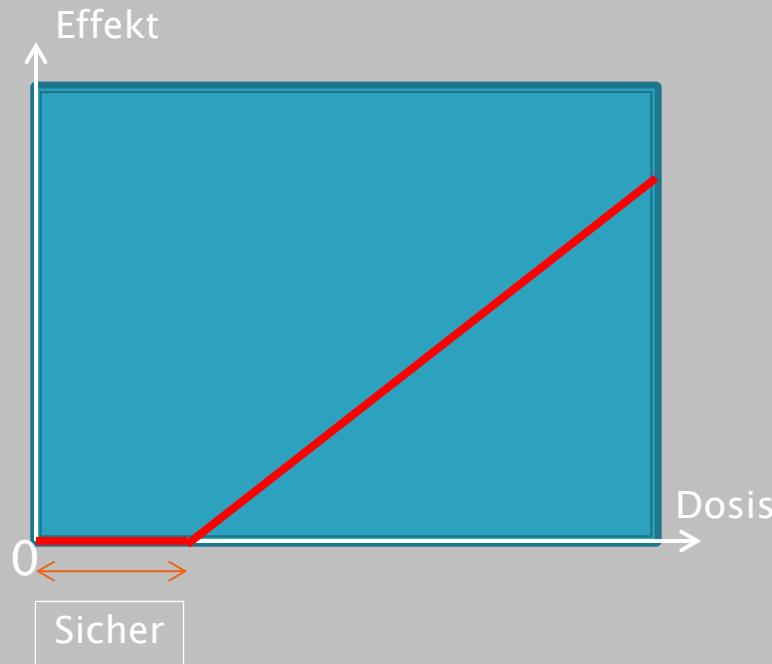
Essen und gegessen werden?

Giftwirkungen

- ▶ Hitze und Kälte, ionisierende Strahlen
- ▶ Säuren und Laugen
- ▶ Oxidantien
- ▶ Lösemittel
- ▶ Proteasen
- ▶ ...
- ▶ Je mehr, desto schlimmer

Dosis–Wirkungsbeziehung

► Mit Schwellenwert



► Ohne Schwelle

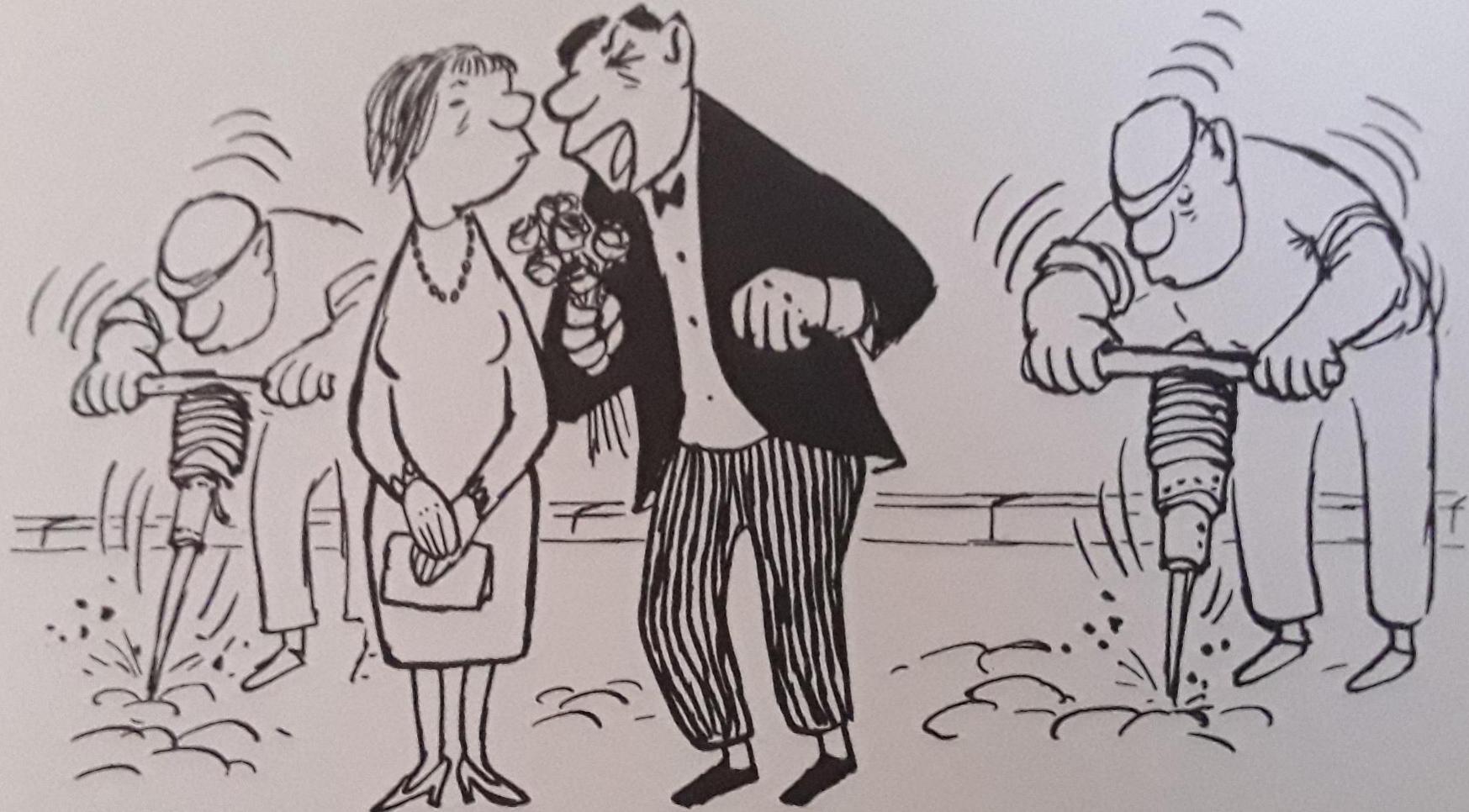


Dosis macht das Gift

- ▶ Paracelsus, aber...

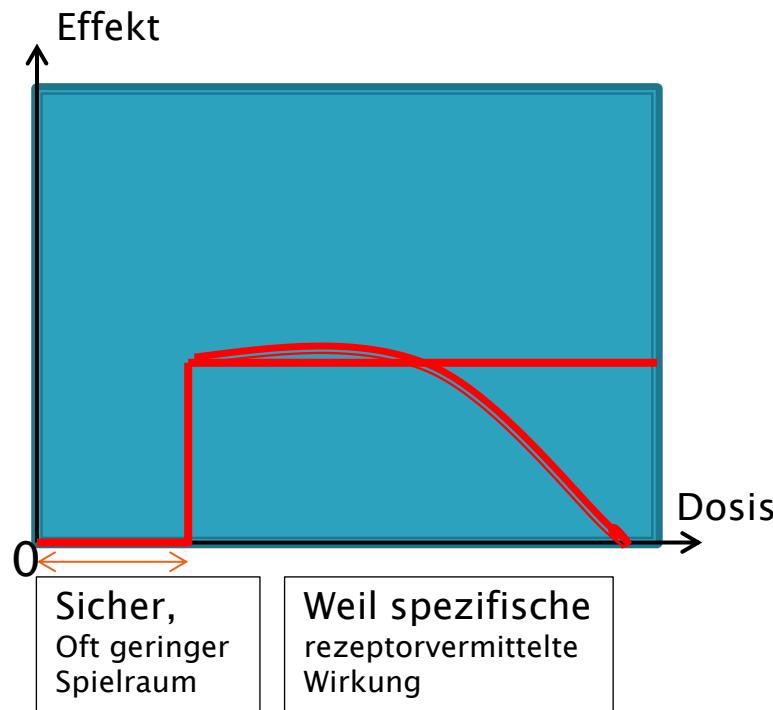


Auch Zeit und Ort entscheidet



Information \neq dosisabhängig

- ▶ Signalstärke > Rauschen
- ▶ Darüber hinaus entscheidet Inhalt, nicht Stärke



- Gegenregulation
- Rezeptoren-Sättigung
- Toxikologische Tests:
bei hoher Dosis
(Power der Studie)

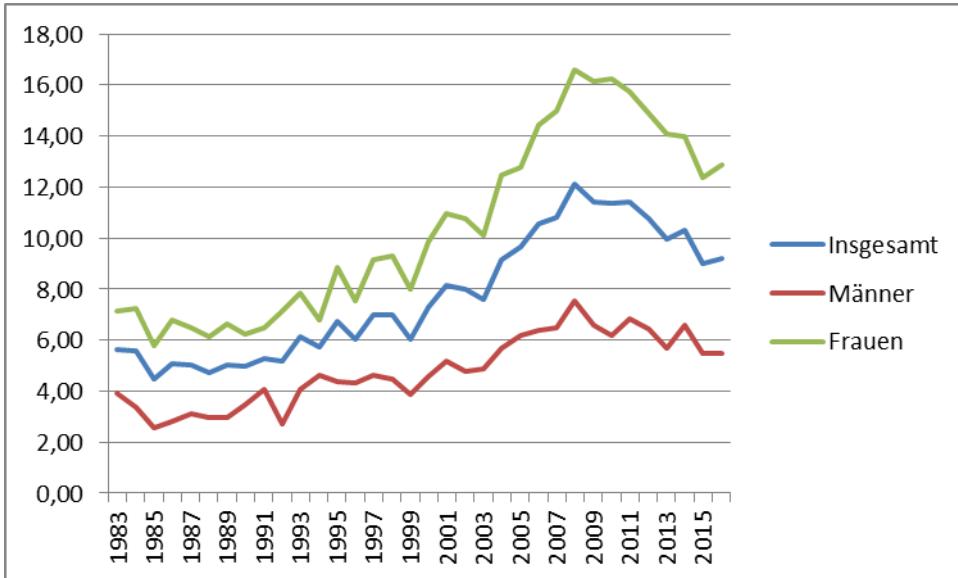
Was ist denn ein Hormon?

- ▶ Kommunikation zwischen Zellen:
 - Zellkontakte
 - Chemische Botenstoffe:
 - „Zelle“ → ganzer Körper: „Hormon“
 - „Zelle“ in einem spezifischen Organ („Drüse“)
 - „irgendwo“: „Gewebshormon“
 - Zelle – Nachbarzelle: Zytokin, Transmitter, ...
 - ▶ Regulation über prä- und postsynaptische Rezeptoren, übergeordnete Regelkreise,...

Einige Beispiele:

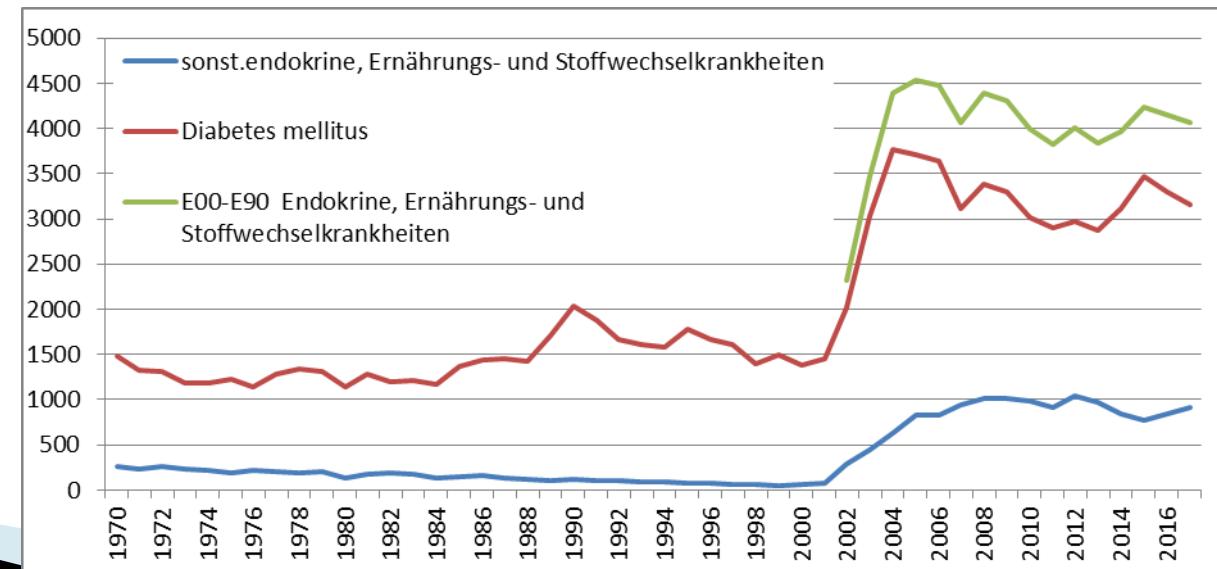
- ▶ Trends in SD-Krankheiten
- ▶ Beispiel Spermiogramm
- ▶ BPA-Story
- ▶ Adipogene
- ▶ Kindersegen: Seveso, Linz und Kaffee
- ▶ Phthalate und AGD

Trends in SD-Krankheiten



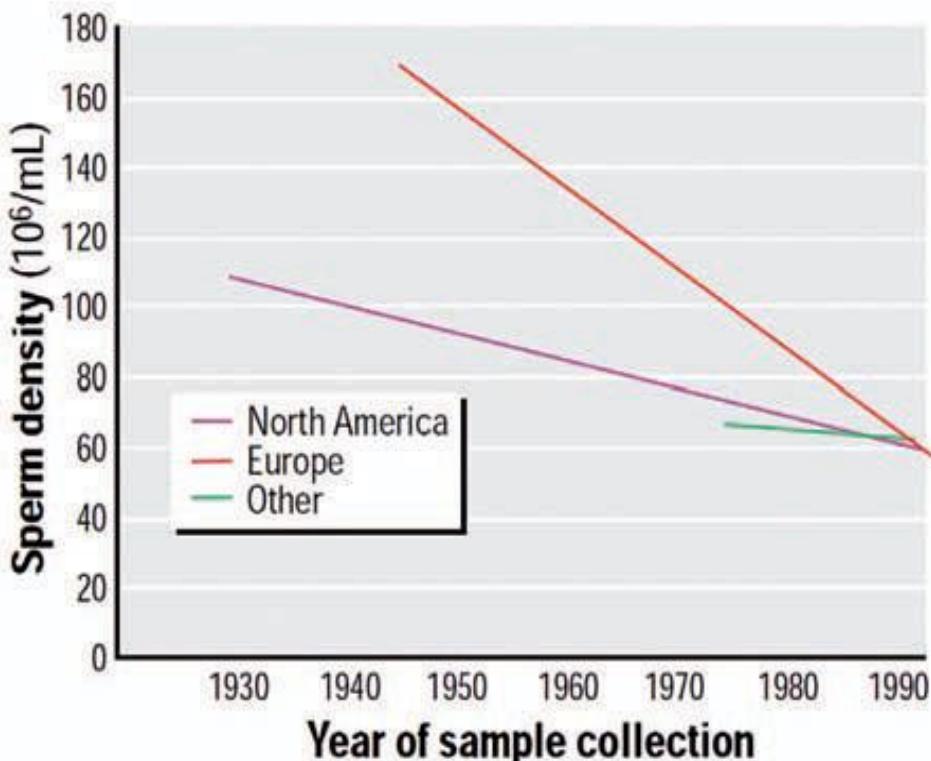
Schilddrüsenerkrankungen – Inzidenz:
altersstandardisierte Rate,
Jeweils auf 100.000 Personen / Männer / Frauen,
Europäische Standardbevölkerung 2013.

Todesursachen:
Absolute Zahlen



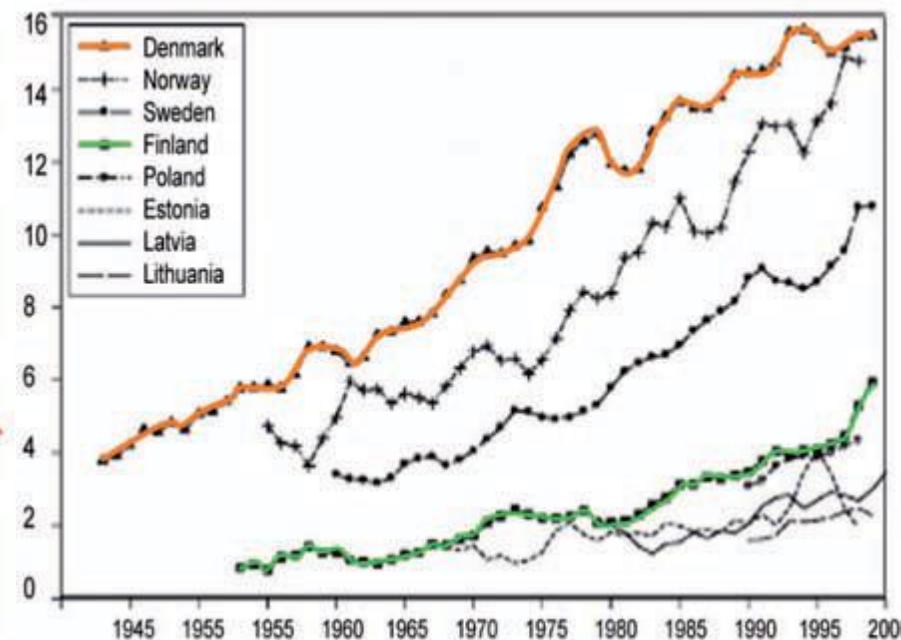
Aber...

Male fertility



Interactive regression model for mean sperm density by year and geographic region after controlling for proven fertility (from ref. 16).

(16) Swan SH, Elkin EP, Fenster L. The question of declining sperm density revisited: an analysis of 101 studies published 1934–1996. Environ Health Perspect 2000; 108:961–6.

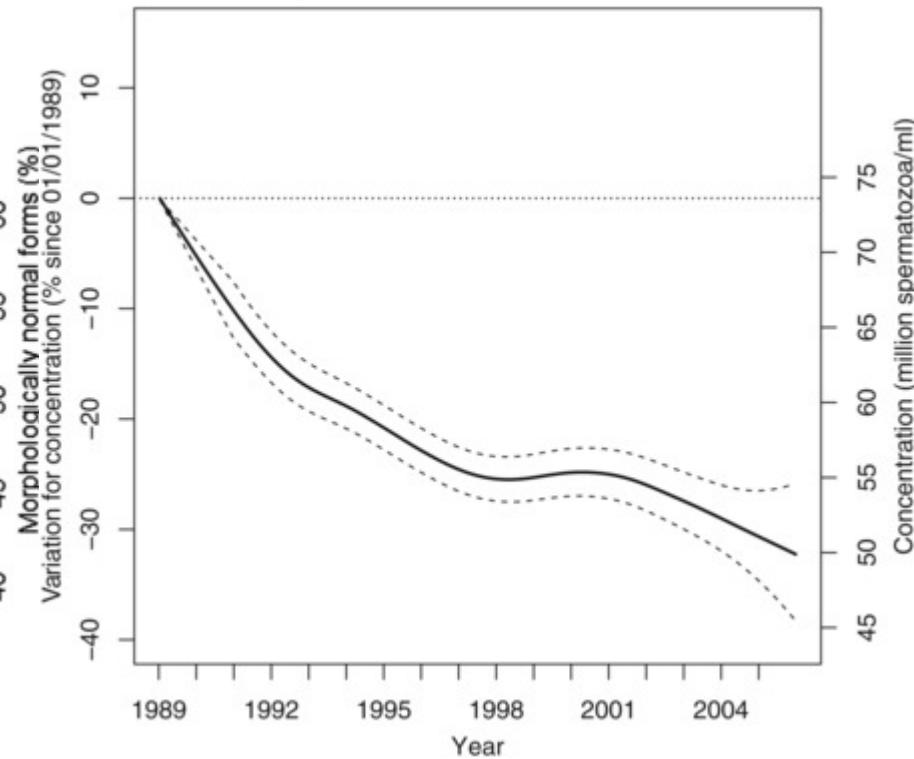
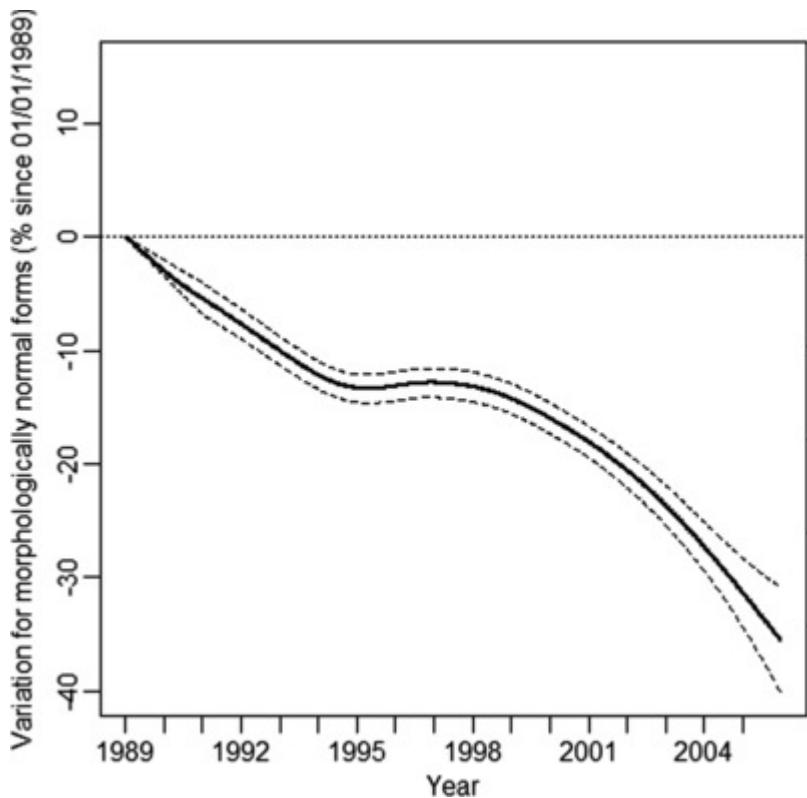


Trends in incidence of testicular cancer in Northern Europe. Age-standardised (world standard population) incidence of testicular cancer by year of diagnosis, country and histological type (from ref. 30).

(30) Richiardi L, Bellocchio R, Adami HO, Torrang A, Barlow L, Hakulinen T et al. Testicular cancer incidence in eight northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev 2004 December; 13:2157–66.

Spermiogramm

M. Rolland, J. Le Moal, et al.
Hum Reprod. 2013 Feb; 28(2): 462–470.



Among a sample of 26 609 partners of totally infertile women undergoing an assisted reproductive technology (ART) procedures in the whole of France over a 17-year period, there was a continuous decrease in semen concentration of about 1.9% per year and a significant decrease in the percentage with morphologically normal forms but no global trend for motility.

Intrauterin position effect

Neuroscience and Biobehavioral Reviews 26 (2002) 665–678

Review

Intrauterine position effects

Bryce C. Ryan*, John G. Vandenberg

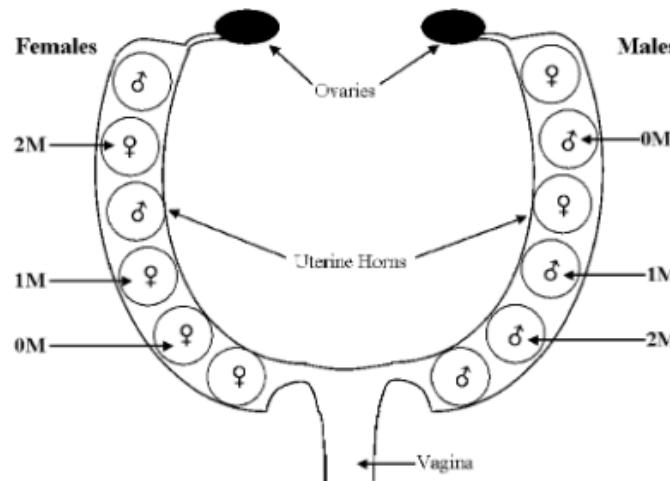


Fig. 1. Schematic illustrating fetus positions in a womb. The 0M–2M

2.5. Secondary sex ratio

IUP alters secondary sex ratios (i.e. the ratio of male pups to female pups at birth). As adults, 2M female gerbils give birth to almost 60% male pups. Conversely, 0M females, and singleton females, give birth to about 40% male pups. 1M mothers produce the traditional 50% sex ratio [11,15, 16,23]. Similar reproductive outputs are also seen in mice [50,104,105]. These effects do not seem to be caused by selective cannibalism because the litter sizes of 0Ms and 2Ms are similar, and the ratios remain if the pups are delivered via a cesarean section. The mechanism behind this phenomenon is unknown, however, the timing of insemination may cause these shifts in the sex ratio. Female rats

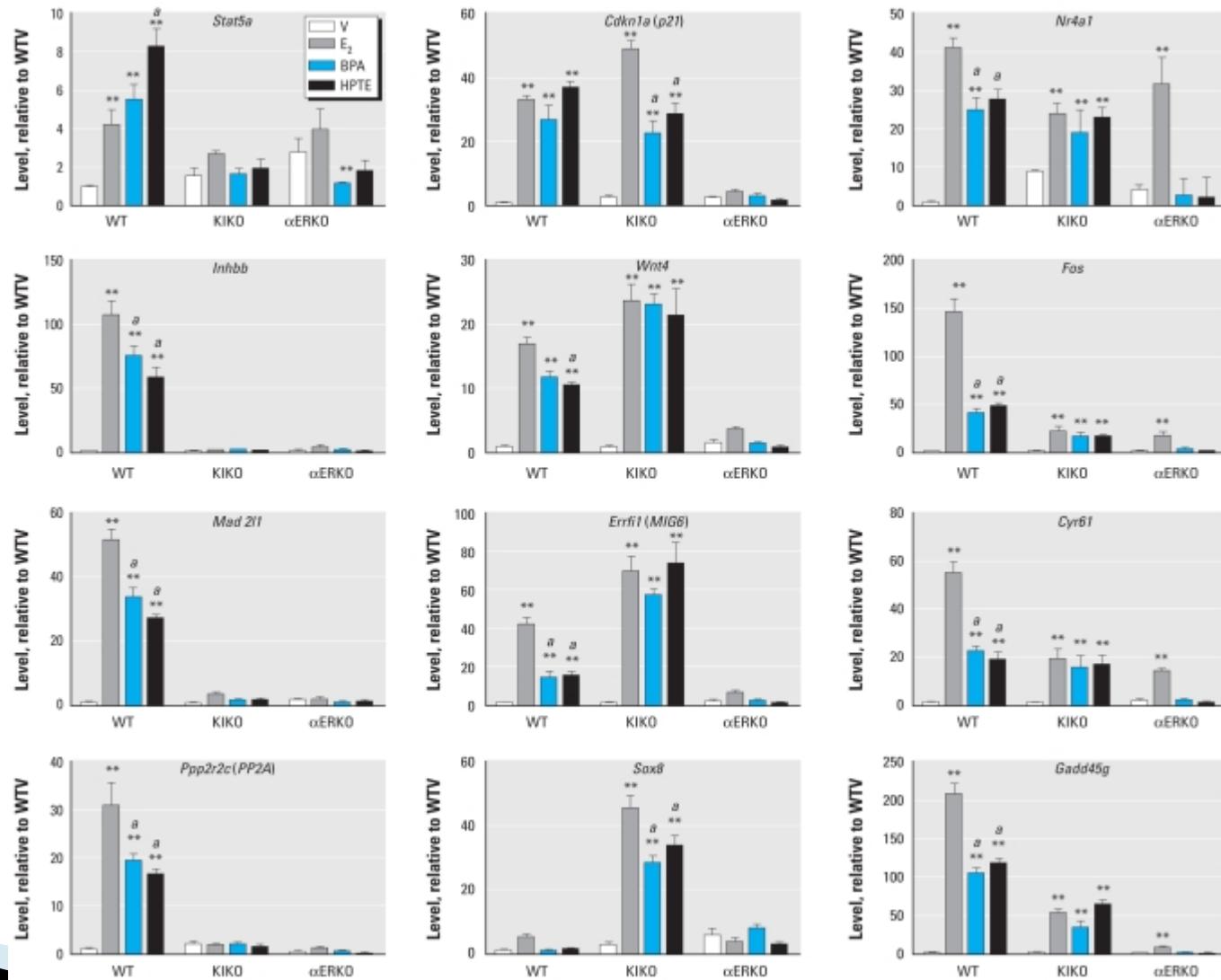
Contents

1. Introduction
2. Physiology
2.1. Hormone levels
2.2. Sensitivity to testosterone
2.3. Enzyme levels
2.4. Reproduction
2.5. Secondary sex ratio
2.6. Asynchronous development
2.7. Environmental estrogens
3. Morphology
3.1. Anogenital distance
3.2. Reproductive organs
3.3. Other morphology
4. Behavior
4.1. Aggression
4.2. Territoriality
4.3. Diet
4.4. Sexual behaviors
5. IUP effects on other species
6. Stress
7. Discussion
Acknowledgements
References

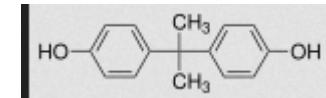
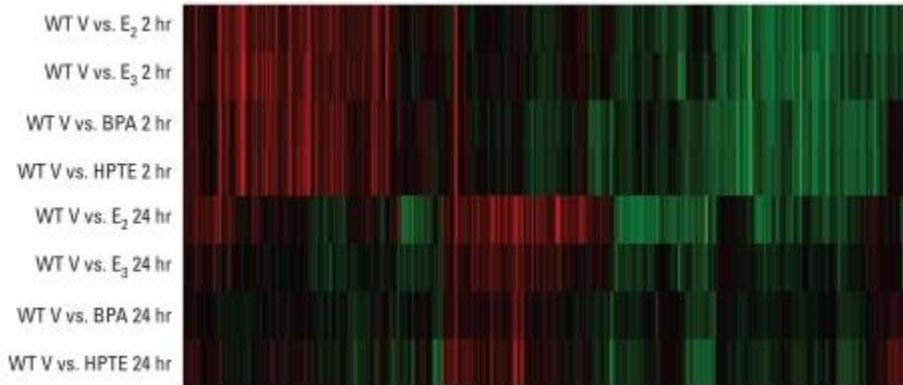
BPA-Story

SC Hewitt et al.
Environ Health Perspect. 2011 Jan; 119(1): 63–70.

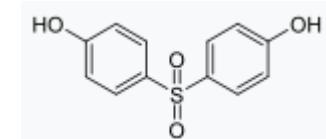
Both xenoestrogens, BPA and HPTE, showed profiles highly correlated to that of E2 in the early response phase (2 hr), but the correlation diminished in the later response phase (24 hr), similar to the known weak estrogen E3. Both xenoestrogens also mimicked E2 in samples from KIKO mice, indicating that they are able to utilize the indirect tethering mode of ER α signaling. No response was detected in ER α -null uteri, indicating that ER α mediates the responses.



BPA contd.



BPA



BPS

BPA ursprünglich als synthetisches Östrogen entwickelt.
Dann kam der DES-Skandal und überhaupt war BPA
nicht sehr gut in Lösung zu halten (Polymerisierung!)

Seit BPA ins Gerede kam, wird es durch BPS und andere
Bisphenole ersetzt.

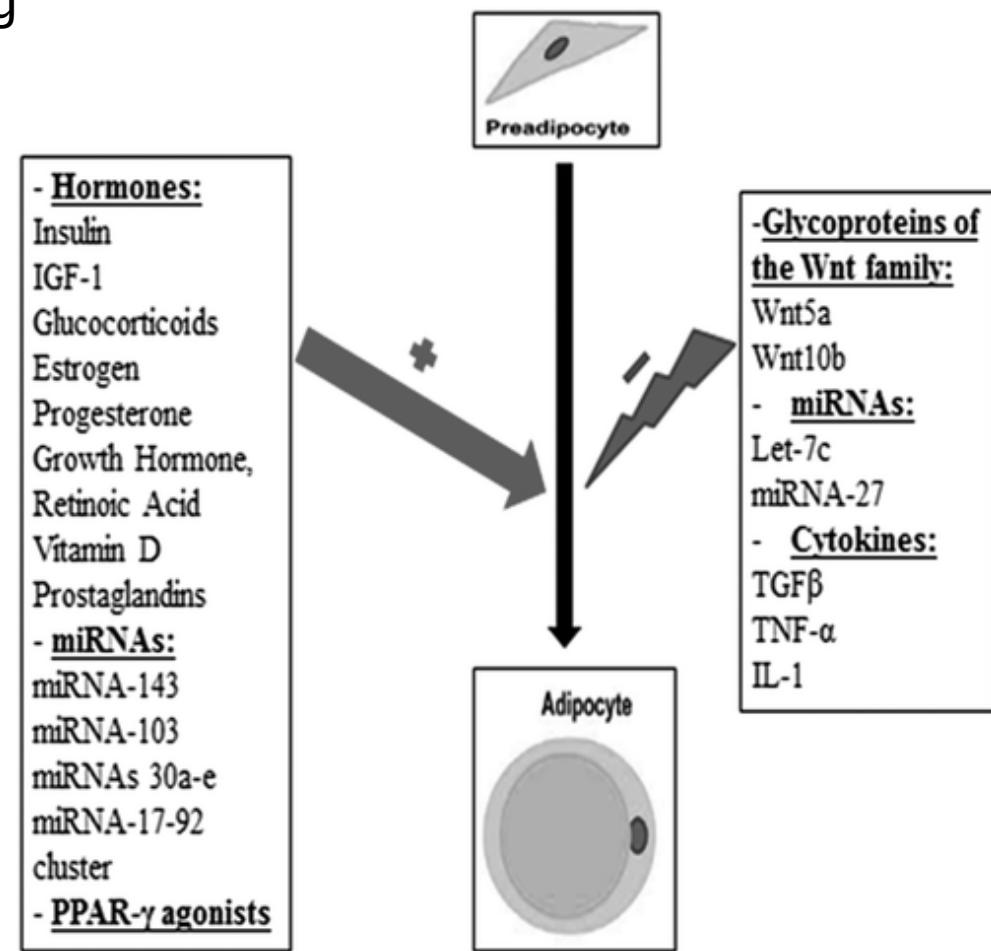
Epidemie in Fettleibigkeit!

Ayman El-Sayed Shafei et al. (2018)

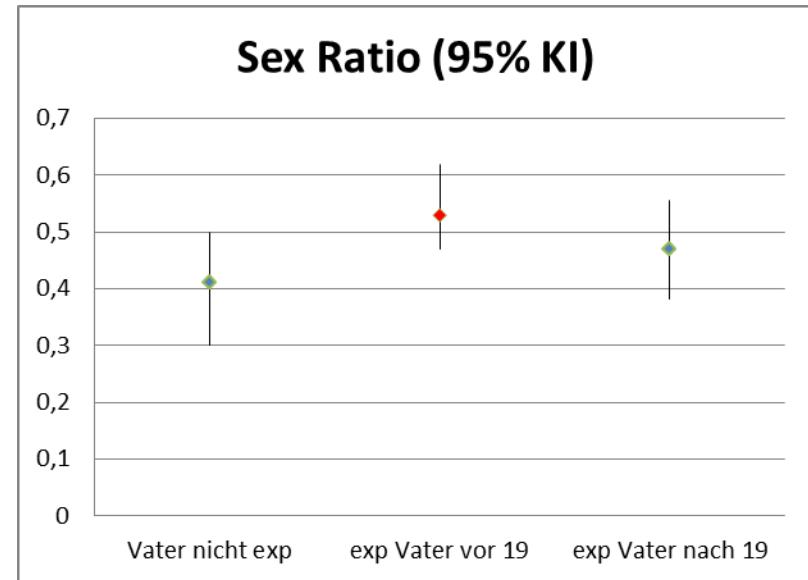
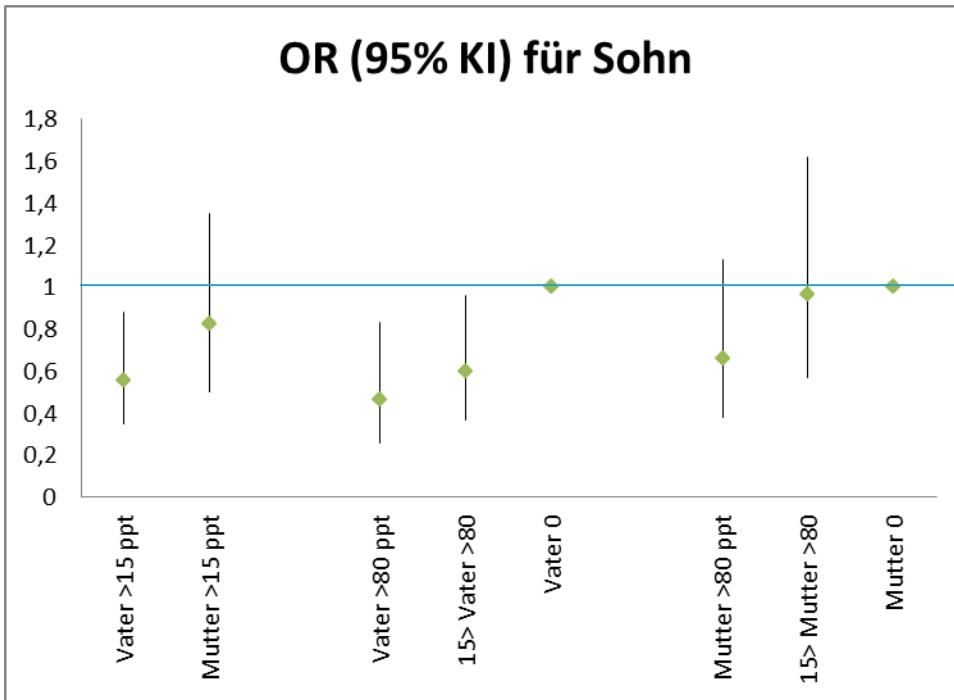
Prenatal Exposure to Endocrine
Disruptors and Reprogramming
of Adipogenesis: An Early-Life
Risk Factor for Childhood
Obesity.

Childhood Obesity 14(1):18ff

Aber:
Fettleibigkeit hat
viele Ursachen!



Heimat bist du großer Söhne?

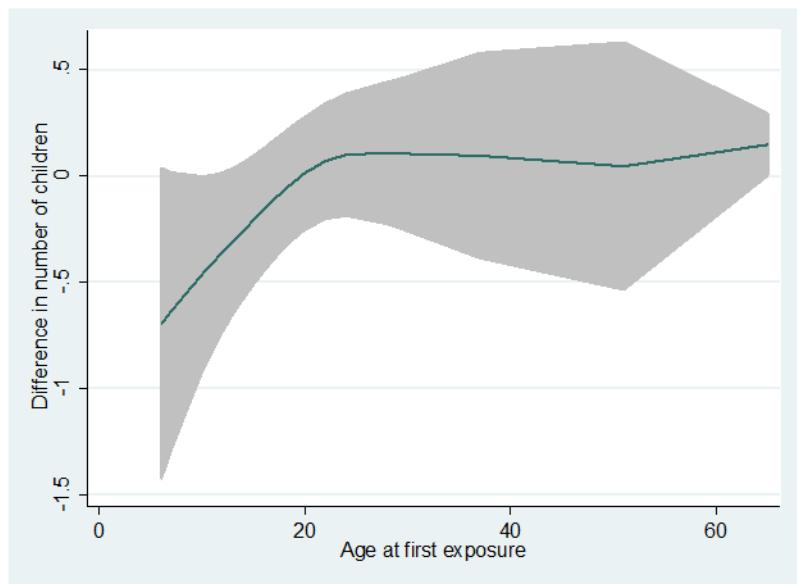
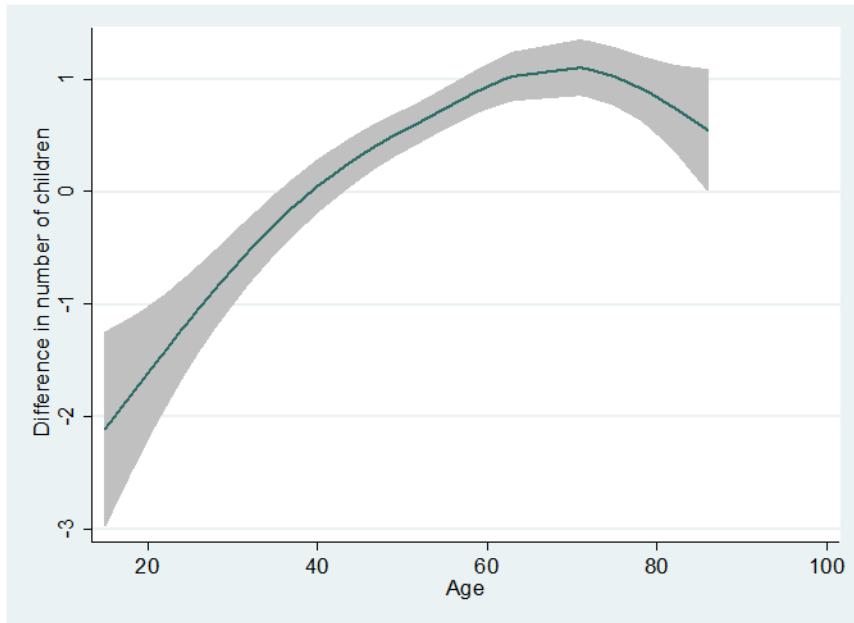


Paolo Mocarelli et al. Paternal concentrations of dioxin and sex ratio of offspring.
THE LANCET • Vol 355 • May 27, 2000, pp. 1858–63

Linzer Kohorte

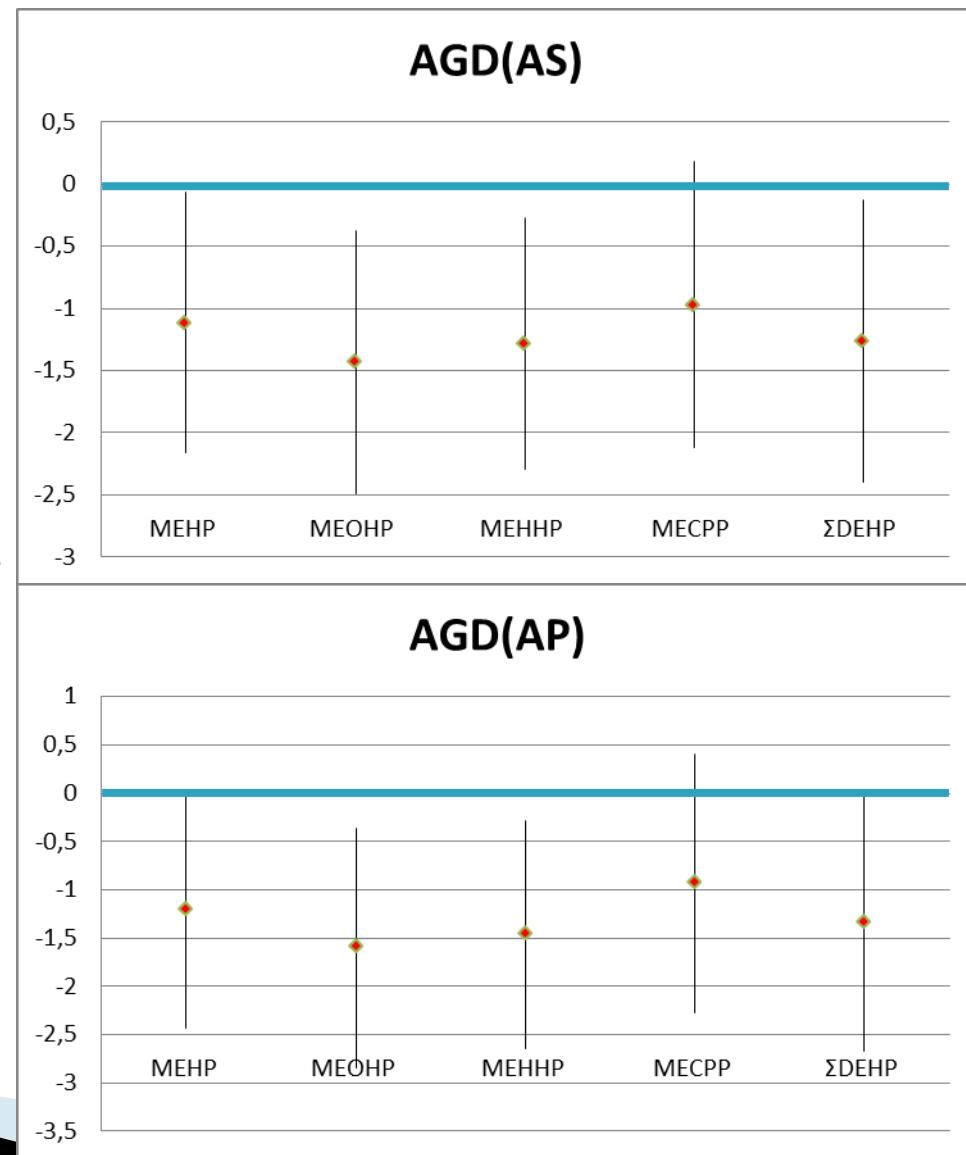
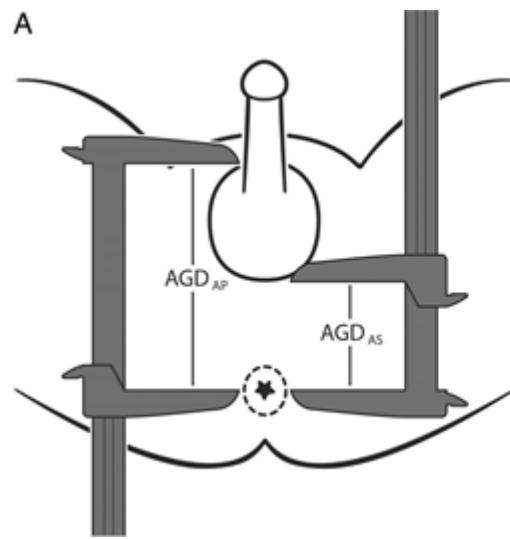


Kaffearbeiter (DR)



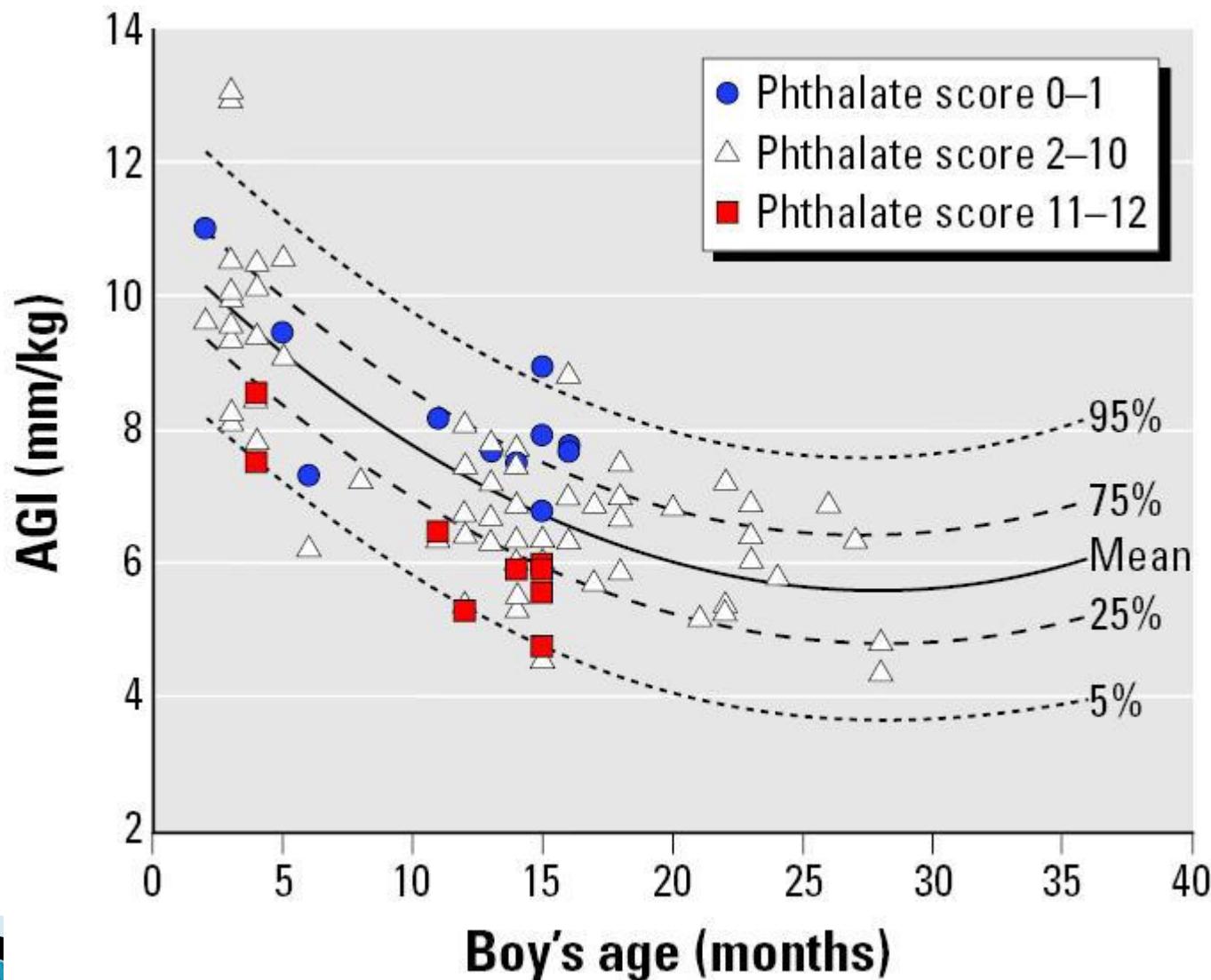
Swan et al.

First trimester phthalate exposure and anogenital distance in newborns
Human Reproduction, Volume 30, Issue 4, 1 April 2015, Pages 963–972



Swan et al.

Environ Health Perspect. 2005 Aug;
113(8): 1056-1061.



Was lernen wir daraus?

- ▶ Oft alte Schadstoffe
- ▶ Aber neuer Wirkmechanismus
- ▶ Nicht die Dosis, sondern der Zeitpunkt!
- ▶ Generationenübergreifende Wirkung
 - Schwierig mit Berufskrankheitskonzept
- ▶ Viele mögliche relevante Endpunkte
 - Multikausal, daher schwer nachzuweisen
- ▶ Epidemiologie und Toxikologie kombinieren